Transdermal drug delivery system for non-steroidal anti inflammatory drugs: A review

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ABSTRACT
For the treatment of pain and inflammation Non-steroidal anti-inflammatory drugs are the most frequently used medications, but because of number of side effects limit their uses. Transdermal drug delivery system (TDDS) provides sustain drug release for systemic as well as local treatment and reduces the side effects associated with its oral therapy. Transdermal delivery of NSAIDs has advantages of avoiding hepatic first pass effect, drug degradation in GIT, specific problems associated with the drug like gastric irritation and lower absorption. By TDDS of NSAIDs can be deliver the drug for extended period of time at a sustained level. The present article gives the brief view on the formulation, development and evaluation been done on various NSAIDs transdermal patches to reduce the side effects associated with the oral delivery. The various NSAIDs included in this article are Diclofenac Acid, Aceclofenac, Lornoxicam, Celecoxib, Ketoprofen, Ibuprofen Naproxen, Indomethacin, Ketorolac, Meloxicam, Tenoxicam. Transdermal delivery of NSAIDs has advantages over oral delivery by avoiding hepatic first pass effect, drug degradation in GIT, dose dumping, specific problems associated with the drug like gastric irritation and lower absorption and hence increases the patient compliance. The market of transdermal product has been in significant upward trend and likely to continue in future.

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INTRODUCTION

A medicated adhesive pad that is placed on the skin to deliver a timed-release dose of medication through the skin into the bloodstream called skin patch. Generally refers to Transdermal Patch or Transdermal Drug Delivery system (TDDS). TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver, provides constant blood levels, avoids first pass metabolism, and avoids dose dumping. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose.

Limitation of transdermal patch is principally associated with barrier function of skin. The molecular weight of drug should be reasonable, and that it should have adequate solubility in both lipophilic and aqueous environment. Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation.

NSAIDs reduce pain significantly in patients with arthritis, low back pain, and soft tissue pain. NSAIDs reduce pain and inflammation by blocking cyclo-oxygenases (COX), enzymes that are needed to produce prostaglandins. Most NSAIDs block 2 different cyclo-oxygenases, COX-1 and COX-2. COX-2, found in joints and muscle, contributes to pain and inflammation. However, NSAIDs have important adverse effects, including gastrointestinal bleeding because they block the COX-1 enzyme, which protects the lining of the stomach from acid, and also associated with peptic ulcer disease, hypertension, edema, and renal disease. NSAIDs when applied topically in the form of transdermal patch, without reaching higher plasma drug concentrations the drug penetrate the skin, subcutaneous fatty tissue, and muscle in amounts sufficient to exert local therapeutic effects. Hence NSAIDs offer the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse events.

Drug Penetration across Human Skin

Drug molecules can penetrate through the skin by.

- Sweat ducts
- Hair follicles
- Sebaceous glands
- Directly across the stratum corneum.

Suitability Criteria for Drugs to be formulated as Transdermal Drug Delivery System

- Physiochemical properties of drug must allow it to be absorbed percutaneously, this means its molecular weight should be reasonable and less than 500 Da.
- Should have adequate solubility in both lipophilic and aqueous environment.
- Exhibit low half-life less than 10hours.
- Exhibit low oral bioavailability.
- Should exhibits the partition coefficient log P in the range of 1.0 to 4.0
- The drug must not be locally irritating or sensitizing.
- Exhibit low therapeutic index.
Events to Take Place during Drug Transport

Figure 1. A multilayer skin model showing the sequence of transdermal permeation

The phenomenon of percutaneous absorption (or skin permeation) can be visualized as consisting of a series of steps in sequence: sorption of a penetrant molecule onto the surface layers of stratum corneum, diffusion through it and the viable epidermis, and finally, at the papillary layer of the dermis, the molecule is taken up into the microcirculation for subsequent systemic distribution. The viable tissue layers and the capillaries are relatively permeable, and the peripheral circulation is sufficiently rapid, so that for the great majority of penetrants, diffusion through the stratum corneum is often the rate-limiting step. The stratum corneum acts as a passive, but not an inert, diffusion medium. No active transport process has been shown to be involved in skin permeation.

Advantages of Transdermal Patch

- Avoidance of first pass metabolism of drugs.
- Avoidance of Degradation of drug in GIT.
- Reduced plasma concentration levels of drugs, with decreased side effects.
- Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index.
- Easy elimination of drug delivery in case of toxicity.
- Reduction of dosing frequency an enhancement of patient compliance.
- Transdermal medications deliver a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failure frequently associated with intermittent dosing can also be avoided.
- Delivery of drug through transdermal patch can increase the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to ‘hepatic first pass’ effect.
- Due to above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
- The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.
- Can be easily applied to paediatric, elderly and mentally disabled patient.
- Transdermal patch can be self-applied to the patient.
Limitations of Transdermal Patch\(^{(2)}\)

- Limitation of transdermal patch is principally associated with barrier function of skin.
- The molecular weight of drug should be reasonable, and that it should have adequate solubility in both lipophilic and aqueous environment.
- Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation.

Types and Method of Formulation of Transdermal Patches\(^{(2,8)}\)

Four different approaches have been utilized to obtain transdermal drug delivery systems:

Matrix Diffusion-Controlled Systems

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. The drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc. The advantage of this system is the absence of dose dumping since polymer cannot rupture.

![Figure 2-Matrix controlled drug delivery system](image)

Membrane Permeation-Controlled Systems

In this type of system, the drug reservoir is totally encapsulated in a shallow Compartment moulded from a drug- impermeable metallic plastic laminate and a rate controlling membrane, which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium such as Silicone fluid to form a paste like suspension. The major advantage of membrane permeation controlled transdermal system is the constant release of drug. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.
Figure 3- Membrane controlled transdermal delivery system

**Adhesive Dispersion-Type Systems**

This system is a simplified form of the membrane permeation-controlled system. Here the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g., poly (isobutylene) or poly (acrylate) adhesive and then Spreading the medicated adhesive, by solvent casting or hot melt, on to a sheet of drug Impermeable metallic plastic backing to form a thin drug reservoir layer.

Figure 4- Adhesive dispersion-type transdermal drug delivery system

**Micro-Reservoir Type or Micro-Sealed Dissolution Controlled Systems**

This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-soluble liquid polymer and then dispersing the drug suspension homogenously in lipophilic polymer viz. Silicone elastomers by high energy dispersion technique to form several discrete, unleachable microscopic spheres of drug reservoirs.
Components Transdermal Patch (8,9,10,11)

1. Polymer Matrix

The following criteria should be satisfied for a polymer to be used in transdermal patches.

- Molecular weight, physical characteristics and chemical functionality of the polymer must allow the diffusion of drug substance at desirable rate.
- The polymer should be stable.
- The polymer should be nontoxic.
- The polymer must be easy to manufactured and fabricate into the desired product.
- The polymer should be inexpensive.
- The polymer and its decomposed product must be non-toxic or non-antagonistic to the host.
- Large amounts of the active agent are incorporated into it.

2. Drug

2.1 Physiochemical Properties

- The drug should have a molecular weight less than 500 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases.
- The drug should have a low melting point.

2.2. Biological Properties

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half-life ($t_{1/2}$) of the drug should be short.
- The drug must not produce allergic response.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal patches.
3. Permeation Enhancers

Chemicals that promote penetration of topically applied drugs are commonly referred to as accelerants, absorption enhancers or penetration promoters. A prime research objective is to identify chemicals that significantly enhance the drug penetration through the epidermis but not severely irritate or damage the skin. Some of the properties of such chemical permeation enhancers and the desirable attributes have been described. These chemicals ideally should be safe and non-toxic, pharmacologically inert, non-irritant and non-allergenic.

4. Solvent

These compounds increase penetration possibly by swelling the polar pathway.

E.g.: Water alcohols—Methanol & ethanol, Dimethyl acetamide Propylene glycol and Glycerol.

5. Excipients

5.1. Adhesives

The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.

- It should not be irritant
- It should be easily removed
- It should not leave an unwashable residue on the skin
- It should have excellent contact with the skin.
- Physical & chemical compatibility with the drug
- Permeation of drug should not effect.

5.2. Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. Typically liners are composed of a base layer which may be Non-occlusive (e.g. Paper fabric) or occlusive (polyethylene, polyvinylchloride).

5.3. Backing

Protect the patch from the outer environment. Backing membrane are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top accept printing.

E.g. Metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil) etc.

**Factor Effecting Transdermal Permeability**

Physico-Chemical properties of the penetrant molecules.

1. **Partition Coefficient.**

Drug having both lipid and water solubility are favorable absorbed through the skin. A lipid/water partition coefficient equal to or more than one is generally required.

2. **pH**

A very high and low pH value can be destructive to the skin. With moderate pH values the flux of ionisable drug can be affected by change in pH as these alter the ratio of charged to uncharged species and their transdermal permeability.
3. Penetrant Concentration

Increasing concentration of dissolved drug cause proportional increase in flux. At higher concentration, excess solid drug function as reservoir and help to maintain a constant drug concentration for a prolonged period of time

**Physicochemical Properties of Transdermal Drug Delivery Systems**

1. Release Characteristics
Solubility of the drug in the vehicle determines the release rate. Drug release depends on-Whether the drug molecules are dissolved or suspended in the delivery system The interfacial partition coefficient of the drug from the delivery system to skin, pH of the vehicle.

2. Enhancement of Transdermal Permeation
Majority of drugs will not penetrate the skin to reach the therapeutic level. The permeation can be improved by the addition of permeation enhancer into the system.

**Physiological and Pathological Conditions of Skin**

1. Reservoir Effect of Horny Layer
   The horny layer especially the deeper layer can sometimes act as a depot and modify the transdermal permeation of drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin

2. Lipid Film
   The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3. Skin Hydration
   Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin. Increased hydration appears to open up the dense, closely packed cells of the skin and increases its porosity.

4. Skin Temperature
   Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity

5. Regional Variation
   Difference in nature and thickness of the barrier layer of skin causes variation in permeability

6. Pathological Injuries to The Skin
   Injuries that disrupt the continuity of the stratum corneum increases permeability due to increased vasodilatation caused by removal of the barrier layer.

7. Cutaneous Self-Metabolism
   Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and influence the topical bioavailability of the drug.

**Evaluation Parameters for Transdermal Patch**
Transdermal patch is evaluated for the following parameters

- Thickness of the patch
- Weight uniformity
- Folding endurance
• Percentage Moisture content
• Percentage Moisture uptake
• Tensile strength
• Percentage Elongation Break Test
• Drug content
• In-vitro release study
• Ex-vivo absorption study

1. **Thickness of Patch** \(^{(13)}\)
   The thickness of each patch is measured by using screw gauge at different positions of the patch and the average should be calculated.

2. **Weight Uniformity** \(^{(14)}\)
   The weights of number of patches will be taken and the weight variation can be calculated.

3. **Folding Endurance** \(^{(15, 16)}\)
   The numbers of times the film was folded at the same place without breaking give the value of the folding endurance.

4. **Percentage Moisture Content** \(^{(16, 17)}\)
   The prepared patch weighs individually and keeps in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the patch reweighed and can determine the percentage moisture content from the below mentioned formula:

\[
\text{Percentage moisture content} = \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}}\right) \times 100.
\]

5. **Percentage Moisture Uptake** \(^{(16, 17)}\)
   The weighed patch keeps in desiccators at room temperature for 24 h containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 h, the patch reweighed and can determined the percentage moisture uptake from the below mentioned formula.

\[
\text{Percentage moisture uptake} = \left(\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}}\right) \times 100.
\]

6. **Tensile Strength** \(^{(18)}\)
   The tensile strength of transdermal patch is determined by an apparatus designed in such a way that it contains a horizontal wooden platform with fixed scale and attachment of two clips that holds transdermal patch under test. Out of two clips one should fixed and other should be movable. Weights will be hanged to one end of pulley will be attached with movable clip. Three strips of patch cut into 2cm length and 2cm breadth. The breakage of patch can be observed and total weights taken were used for calculation. The tensile strength can be calculated by using following formula.

\[
\text{Tensile strength} = \frac{\text{Total Elongation}}{\text{Original Length}} = \frac{L - L_0}{L_0}
\]

Where, \(L\) = Length after force was applied
\(L_0\) = Original Length
7. Percent Elongation at Brake \(^{18}\)

The percentage elongation break can be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

\[
\text{Elongation percentage} = \left(\frac{L_1 - L_2}{L_2}\right) \times 100,
\]

Where \(L_1\) is the final length of each strip, and \(L_2\) is the initial length of each strip.

8. Drug Content \(^{19}\)

A specified area of patch should be dissolved in a phosphate buffer solution and stir to dissolve the patch. The content transfer into a volumetric flask and the absorbance of the solution measure at wavelength (\(\lambda_{max}\)) of the drug and determine the drug content.

9. In-Vitro Release Study \(^{17}\)

\(\text{In Vitro}\) drug release study can be performed by using a Franz diffusion cell. The cellulose acetate membrane is most commonly used for the determination of drug from the prepared transdermal patches. The cellulose acetate membrane should mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal patch should be placed on the cellulose acetate membrane and cover with aluminium foil. The receptor compartment of the diffusion cell should be filled with phosphate buffer pH 7.4. The whole assembly can be fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment should be constantly and continuously stir using magnetic beads, and the temperature should be maintain at 32 ± 0.5°C, because the normal skin temperature of human is 32°C. The samples should be withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase should replenish with an equal volume of phosphate buffer at each sample withdrawal.
10. Ex-Vivo Absorption Study

Ex-vivo study can also be carried out by using Franz diffusion cell. Abdominal skin of male Wistar rat can be used in study. Hair from the abdominal region should be removed carefully. The dermal side of the skin should be thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in phosphate buffer pH 7.4 before starting the experiment. The temperature of the cell maintain at 32 ± 0.5°C. The isolated rat skin piece can be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume should be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium should be replaced. Sample can be analyze using spectrophotometer.

Transdermal Patches Containing NSAIDS Drugs

DICLOFENAC ACID

Diclofenac is an acetic acid nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties used to treat pain, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is completely absorbed from the gastrointestinal tract and having half-life of 2 hours. Thus required frequent administration of doses of drug to maintain therapeutic drug level.

Kunal N Patel et al. formulated a matrix type transdermal drug delivery system containing Diclofenac Acid by solvent evaporation. Different concentrations of Labrasol, oleic acid and triacetin were used to enhance the transdermal permeation of diclofenac acid. Formulation containing 5% drug, 85% adhesive solution and 10% triacetin as permeation enhancer showed best in vitro skin permeation through human cadaver skin as compared to all other formulations.

Jadhav. R.T et.al formulated the Transdermal films of Diclofenac Sodium by using different polymer combinations such as hydrophilic (Poly vinyl alcohol: Poly vinyl pyrolidone), and combination of hydrophilic - lipophilic polymers (Ethyl cellulose:Poly vinyl pyrolidone). Films were prepared by the film casting method. In vitro drug release study through cellophane membrane indicates that hydrophilic polymer showed higher release than the hydrophilic - lipophilic combinations.

Priyanka Arora et. al prepared matrix-type transdermal patches containing diclofenac diethylamine using different ratios of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique. All the prepared formulations were subjected to physical studies in vitro release studies and in vitro skin permeation studies. Based on a physicochemical and in vitro skin permeation study, formulation PA4 (PVP/EC, 1:2) and PA5 (PVP/EC, 1:5) were chosen for further in vivo experiments.

ACECLOFENAC

Aceclofenac is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The dose is 100 mg twice daily. Aceclofenac has higher anti-inflammatory action than conventional NSAIDs. It is a cytokine inhibitor. Aceclofenac works by blocking the action of a substance in the body called cyclo-oxygenase. Cyclo-oxygenase is involved in the production of prostaglandins which cause pain, swelling and inflammation.

Rakesh. P. Patel et al have developed a matrix-type transdermal therapeutic system containing drug Aceclofenac with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique by using 15 % w/w of dibutyl phthalate to the polymer weight, incorporated as plasticizer. Different concentrations of oleic acid and isopropyl myristate were used to enhance the transdermal permeation of Aceclofenac. Formulation F9 containing 15 % of oleic acid with 10 %
Isopropyl myristate showed highest flux among all the formulations and 1.369 fold enhancements in drug permeation.

Shankar. M.S et al formulated the matrix-type transdermal patches of Aceclofenac using different ratios of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent evaporation technique using 10% w/w of dibutyl phthalate incorporated as plasticizer. Based on a physicochemical and in vitro skin permeation study, formulation F1 (PVP/EC, 5:1) and F5 (PVP/EC, 1:5) were chosen for further in vivo experiments. The anti-inflammatory effect and a sustaining action of Aceclofenac from the two transdermal patches selected were studied by inducing paw edema in rats with 1% w/v carrageenan solution. Formulation F1 produced 91.04% inhibition of paw edema in rats 10hrs after carrageenan insult, whereas in the case of formulation F5, the value became 43.34% at 10 hrs after the carrageenan insult.

LORNOXICAM

Lornoxicam is a non-steroidal anti-inflammatory drug that belongs to the oxicam class. As with other NSAIDS, lornoxicam is a potent inhibitor of the cyclooxygenase enzymes, which are responsible for catalyzing the formation of prostaglandins and thromboxane from arachidonic acid. This leads to the reduction of inflammation, pain, fever, and swelling, which are mediated by prostaglandins. Lornoxicam Half-life is 3-5 hours. Used for the treatment of acute mild to moderate pain, as well as pain and inflammation of the joints caused by certain types of rheumatic diseases.

K. Kavitha et al developed and evaluated the matrix-type transdermal therapeutic system containing Lornoxicam with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. Three transdermal patch formulations (F1, F2 and F7) consist of Hydroxypropyl methyl cellulose E5 and Ethyl cellulose in the ratios of 5:0, 0:5 and 1:1 respectively were prepared. All formulations carried 4% w/v of Tween-80 as penetration enhancer for Lornoxicam and 10% w/v of Polyethylene glycol as plasticizer in dichloromethane and methanol (4:1) as solvent system. The formulation, F1 (Hydroxypropyl methyl cellulose E5 alone) showed maximum release of 95.76 ± 1.38 % in 8 h, whereas F2 (Ethyl cellulose alone) showed maximum release of 58.64 ± 1.14 % in 24 h. The formulation, F3 with combination of polymers (1:1) showed maximum release of 76.76 ± 2.1 % in 24 h, emerging to be ideal formulations.

Dheeraj T. Baviskar et al developed a matrix-type transdermal drug delivery system of lornoxicam with the addition of ethyl cellulose: polyvinylpyrrolidone and Eudragit RL 100:Eudragit RS 100 in different ratios with propylene glycol as plasticizer (5%) and tween 80 as permeation enhancer using the solvent evaporation technique. The formulations showing best results (A3 and B3) were selected further for in vivo and pharmacokinetic studies on animals.

CELECOXIB

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme.

S Jayaprakash et al prepared transdermal patch of celecoxib by using different polymers such as hydroxyl propyl methylcellulose, methylcellulose, Polyvinylpyrrolidone. The in-vitro release of the drug from the formulations were studied using commercial semi permeable membrane. The prepared formulation was subjected to various physicochemical evaluation test, in-vitro dissolution studies, kinetics studies. ex-vivo
diffusion studies by using rat skin, guinea pig skin & pig ear skin and finally in-vivo evaluation studies (the patch F4 HPMC 0.75%, PVP 0.25%) were carried out by using rabbits.

M. Yasmin Begum et al formulated the transdermal patch of celecoxib using polymers such as hydroxy propyl methyl cellulose (15cps), polyvinyl pyrrollidine (15cps), Methyl cellulose (15cps) and dibutyl phthalate 30%w/w, as plasticizer. In vitro dissolution studies were carried out in phosphate buffer pH 7.4 using commercial semi permeable membrane. Ex vivo drug diffusion study was carried out using various biological membranes such as rat skin, guinea pig skin and pig ear.

KETOPROFEN

Ketoprofen is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties inhibit prostaglandin synthesis. Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and alleviate moderate pain. The anti-inflammatory effects may be due to inhibition of COX-2, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Half-life 1.1-4 hours.

Umesh Ramchandani et al developed the transdermal Drug delivery system of Ketoprofen drug with Chitosan Polymer. Chitosan is a Hydrophilic, non-toxic, Poly cationic nature, Biocompatible, biodegradable. Solvent costing method is used for the formulation of transdermal film with modification of chitosan.

Shashikant D. Barhate et al formulated ketoprofen transdermal patches by mercury substrate method using polymer Eudragit RS100, Eudragit RL100, HPMC K100M, HPMC E5 and HPMC K4M. Propylene glycol and oleic acid used as a skin permeation enhancer and dibutyl phthalate and polyethylene glycol-400 used as a plasticizer. It was observed that the formulation containing HPMC E5 showed ideal zero-order release kinetics.

IBUPROFEN

Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties. Used for symptomatic treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and osteoarthritis. May be used to treat mild to moderate pain and for the management of dysmenorrhea. Most common symptoms of overdose are abdominal pain, nausea, vomiting, lethargy; other symptoms of overdose include headache, loss of consciousness, tinnitus, CNS depression, convulsions and seizures.

Shahida Jannat et al formulated the Transdermal films of Ibuprofen using Eudragit L 100, Kollidon SR and their combination were separately prepared by solvent casting method. Drug release was evaluated for eight hours and the release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be independent of the polymer concentration in case of Eudragit L 100. Higher polymer content in the matrix decreased the rate and extent of the drug release because of increased matrix strength and gel formation around the matrix particularly for these formulations containing Kollidon SR. On the other hand, a burst drug release was obtained from films containing Eudragit L 100, while the combination of Eudragit L 100 and Kollidon SR gave an intermediate release profile of Ibuprofen from the transdermal films.

Madhulatha A et al developed sustained release transdermal therapeutic system containing Ibuprofen with different ratios of chitosan, HPMC and combination of chitosan-HPMC by solvent-evaporation technique. Based on the invitro dug permeation studies using rat skin, D4 formulation (0.2% plain chitosan+HPMC) produce 86% drug release in 24 hours.
NAPROXEN

Naproxen is a member of the aryl acetic acid group of nonsteroidal anti-inflammatory drugs. Naproxen has analgesic and antipyretic properties. The mechanism of action of naproxen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. It is mainly used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout. Also for the relief of mild to moderate pain and the treatment of primary dysmenorrhea.

G Parthasarathy et al designed the transdermal drug delivery system of Naproxen with Ethylcellulose and Hydroxy propyl methyl cellulose polymer in various concentrations. Transdermal films were fabricated by matrix technique with various polymer proportions using dibutylphthalate as plasticizer. The release profiles were found to be varied with various concentrations of Ethylcellulose Polymer. The sample of patches prepared with 2:8 and 8:2 ratios of Ethyl cellulose and Hydroxy propyl methyl cellulose shows highest and lowest in-vitro release of Naproxen respectively.

M. S Harsoliya et al formulated the transdermal drug delivery system of Naproxen with Chitosan Polymer for Treatment of Arthritis. Solvent costing method is used for the formulation of transdermal film with modification of chitosan

INDOMETHACIN

Indomethacin is a prostaglandin cyclooxygenase inhibitor that acts on both prostaglandin COX-1 and COX -2. It is used in moderate to severe rheumatoid arthritis including acute flares of chronic disease, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis.

Jaydatt K. Jadhav. et al developed and evaluated the matrix-type Transdermal drug delivery system containing Indomethacin with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The prepared Transdermal patches were evaluated for in vitro release, moisture absorption, moisture loss and mechanical properties. The diffusion studies were performed by using Franz diffusion cells. The formulation, F8 with combination of polymers (3:2) showed maximum release of 75.28% in 24 h.

Ting Li et al formulated the transdermal drug delivery system of indomethacin. MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (i.e. azone, L-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid). The enhancing effects of the permeation enhancers were evaluated using two-chamber side-by-side diffusion cells containing excised rat skin. 5% azone and 5% L-menthol were the permeation enhancers of choice for the percutaneous absorption of indomethacin.

KETOROLAC

Ketotolac used for the short-term (~5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Ketorolac is a nonsteroidal anti-inflammatory drug chemically related to indomethacin and tolmetin. Its antiinflammatory effects are believed to be due to inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid.

Pintu Kumar De et al developed the transdermal matrix patch of ketorolac tromethamine with different proportions of polyvinyl pyrrolidone (PVP) and ethyl cellulose (EC). The prepared transdermal patches were subjected to different physicochemical evaluation. The surface topography of the patches was
examined by scanning electron microscopy (SEM). A correlation between invitro drug-release and in-vitro skin permeation was established.

Rita Bhatta et al formulated the polymeric films of Ketorolac tromethamine by solvent casting method. The films were prepared by using various amounts of Kollidon SR to prolong the drug release with localized action. Some films were also prepared containing certain percent of PEG-6000 along with the drug & polymer. The rate of drug release decreased with increased polymer concentration. About 10% increase in polymer concentration causes 50% decreased drug release. When PEG-6000 was used as a channeling agent in this formulation drug release was increased accordingly but higher concentration of PEG-6000 results in decreasing release rate of drug because of increasing viscosity of the matrix channels.

MELOXICAM
Meloxicam is an nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Meloxicam inhibits prostaglandin synthetase (cyclooxygenase 1 and 2) and leads to a decrease of the synthesis of prostaglandins, therefore, inflammation is reduced. Meloxicam is used to relieve the symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component. It is closely related to piroxicam.

Somasundaram Jayaprakash et al developed a transdermal therapeutic system for meloxicam using various polymers like hydroxy propyl methyl cellulose, ethyl cellulose and polyvinyl pyrrolidone and plasticisers by solvent casting technique. The in vitro release studies revealed that the release was sustained up to 24 hours and it followed zero order kinetics (r2–0.998)

Pallavi Srivastava et al developed transdermal drug delivery system using meloxicam as a model drug. The polymer selected for the study is pectin and various concentration ratios of polymer were used for the fabrication of the matrix diffusion controlled transdermal drug delivery system by solvent evaporation technique. In-vitro release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffer as receptor medium and it showed controlled release of drug.

TENOXICAM
Tenoxicam, an anti-inflammatory agent with analgesic and antipyretic properties, is used to treat rheumatoid arthritis, osteoarthritis, backache, and pain. The anti-inflammatory effects of tenoxicam may result from the inhibition of the enzyme cyclooxygenase and the subsequent peripheral inhibition of prostaglandin synthesis. The side effect of tenoxicam is similar to that of other NSAIDs; it causes epigastric pain, nausea, vomiting, dyspepsia and indigestion and increases the risk of renal failure or bleeding.

Nesseem et.al. Formulated a Transdermal film of tenoxicam with the Eudragit L30 D-55 copolymer with permeation enhancers like polyethylene glycol (PEG) and propylene glycol (PG) incorporated at different concentrations using the casting evaporation technique. Formulation containing effective combination of glycerol (0.25 g), PEG200 (0.5 g), PEG400 (1g) and PG (10%) and 0.5% dispersed drug was further studied. Also, this formula had the highest release value than commercially available gel after 24 h.

CONCLUSION:
The formulation and development of successful Transdermal patch depends on physicochemical properties of drug, proper selection of drug as well as polymers. NSAIDs has number of side effects which are mainly associated with the GIT can be avoided by using TDDS of NSAIDs and improves bioavailability as well improve patient compliance by many fold. The major demerit of this route is that all NSAIDs drugs cannot be given through Transdermal route because the drug should possess certain physicochemical properties which are
prerequisite for the transdermal delivery of drugs and suited to permeate through skin. Transdermal Drug Delivery System has been used as safe and effective device and hence need a lot of progress to be done to deliver the drugs like NSAIDs. In the past two decades, transdermal drug delivery has moved from a clinical reality to the point where it represents a viable diagnostic tool for non-invasive diagnosis. The first challenge of creating effective transdermal system ultimately involves ensuring adequate drug permeability through stratum corneum. However thanks to the development of some innovative permeation enhancement technique interest in transdermal was revived in the present decade. More than 20 transdermal patch containing 13 drug molecules are already available in market.

REFERENCES


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